Renal Denervation: State of the Art in 2023

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Disclosure Statement of Financial Interest

None

(Site PI for the RADIANCE SOLO/TRIO and RADIANCE CAP)

Resistant Hypertension: Updated Definition

1 BP not at goal* while taking 3 or more antihypertensive medications, including a diuretic if possible

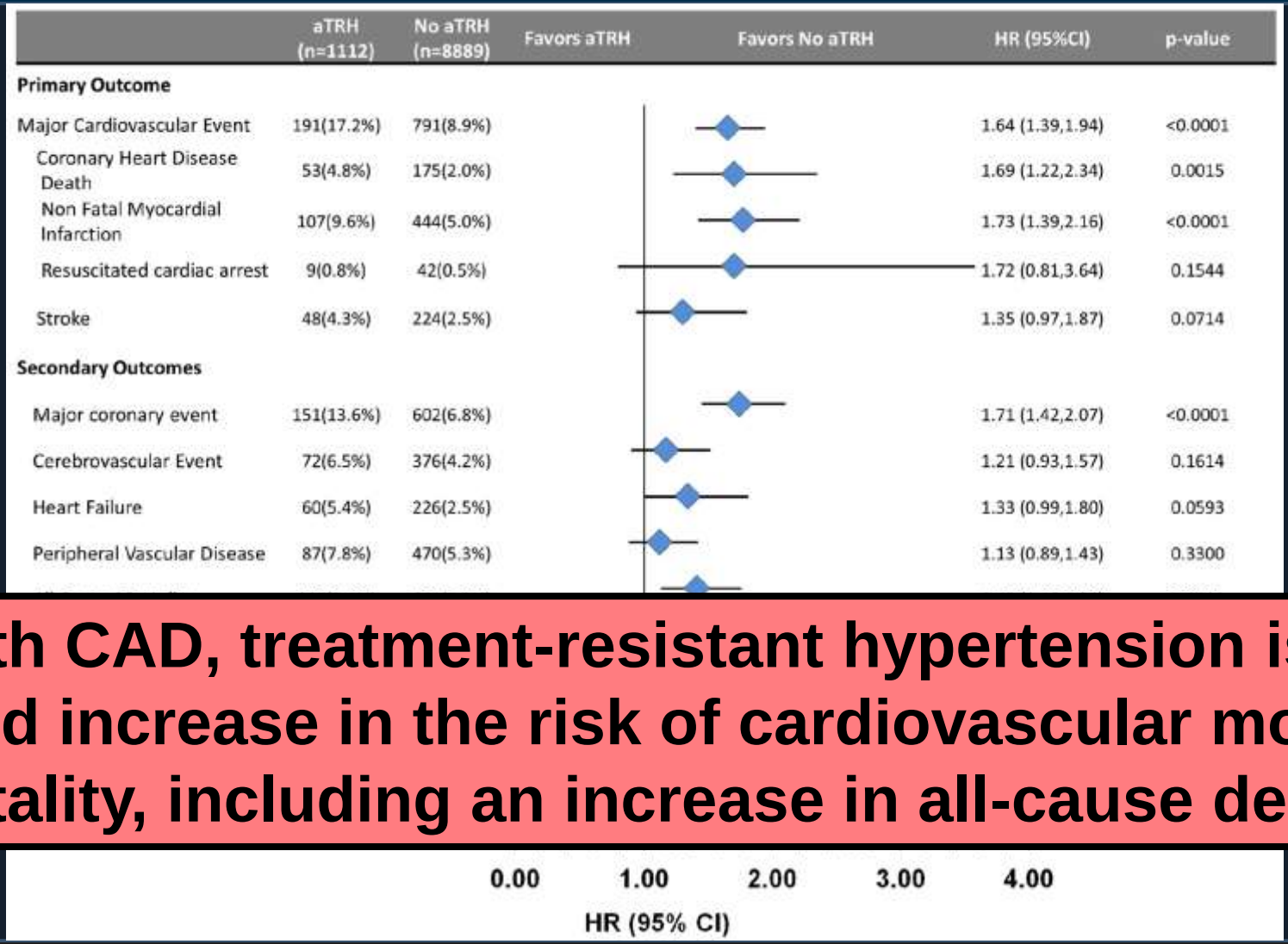
OR

2 BP controlled to goal* using 4 or more antihypertensive medications

*For most patients, the current goal is <130/80 mm Hg

Calhoun DA et al. *Circulation*. 2008;117:e510-526

Resistant Hypertension: Outcomes



In patients with CAD, treatment-resistant hypertension is associated with a marked increase in the risk of cardiovascular morbidity and mortality, including an increase in all-cause death

Bangalore S et al. *AM J Med*. 2014;127(1):71-81

Resistant Hypertension: Outcomes

Table 2. Hazard Ratios for CHD, Stroke, All-Cause Mortality, Combined CHD, Combined CVD, Heart Failure, Peripheral Arterial Disease, and ESRD Comparing Individuals With vs Without aTRH

	Hazard Ratio (95% CI)			
Outcome	Unadjusted	Model 1*	Model 2†	Model 3‡
CHD§	1.42 (1.19–1.69)	1.37 (1.15–1.64)	1.39 (1.16–1.67)	1.44 (1.18–1.76)
Stroke	1.67 (1.30–2.14)	1.49 (1.16–1.91)	1.58 (1.22–2.04)	1.57 (1.18–2.08)
All-cause mortality	1.29 (1.12–1.48)	1.20 (1.04–1.38)	1.27 (1.10–1.47)	1.30 (1.11–1.52)
Combined CHD‖	1.45 (1.27–1.66)	1.45 (1.27–1.66)	1.46 (1.27–1.67)	1.47 (1.26–1.71)
Combined CVD¶	1.50 (1.35–1.66)	1.44 (1.30–1.60)	1.47 (1.32–1.63)	1.46 (1.29–1.64)
ESRD	3.23 (2.66–3.66)	2.57 (1.65–4.65)	2.53 (1.62–4.72)	1.93 (1.11–3.41)

These results demonstrate that aTRH increases the risk for cardiovascular disease and end-stage renal disease

Muntner, Davis, Cushman, Bangalore S et al. *AM J Med*. 2014; 64(5):1012-21

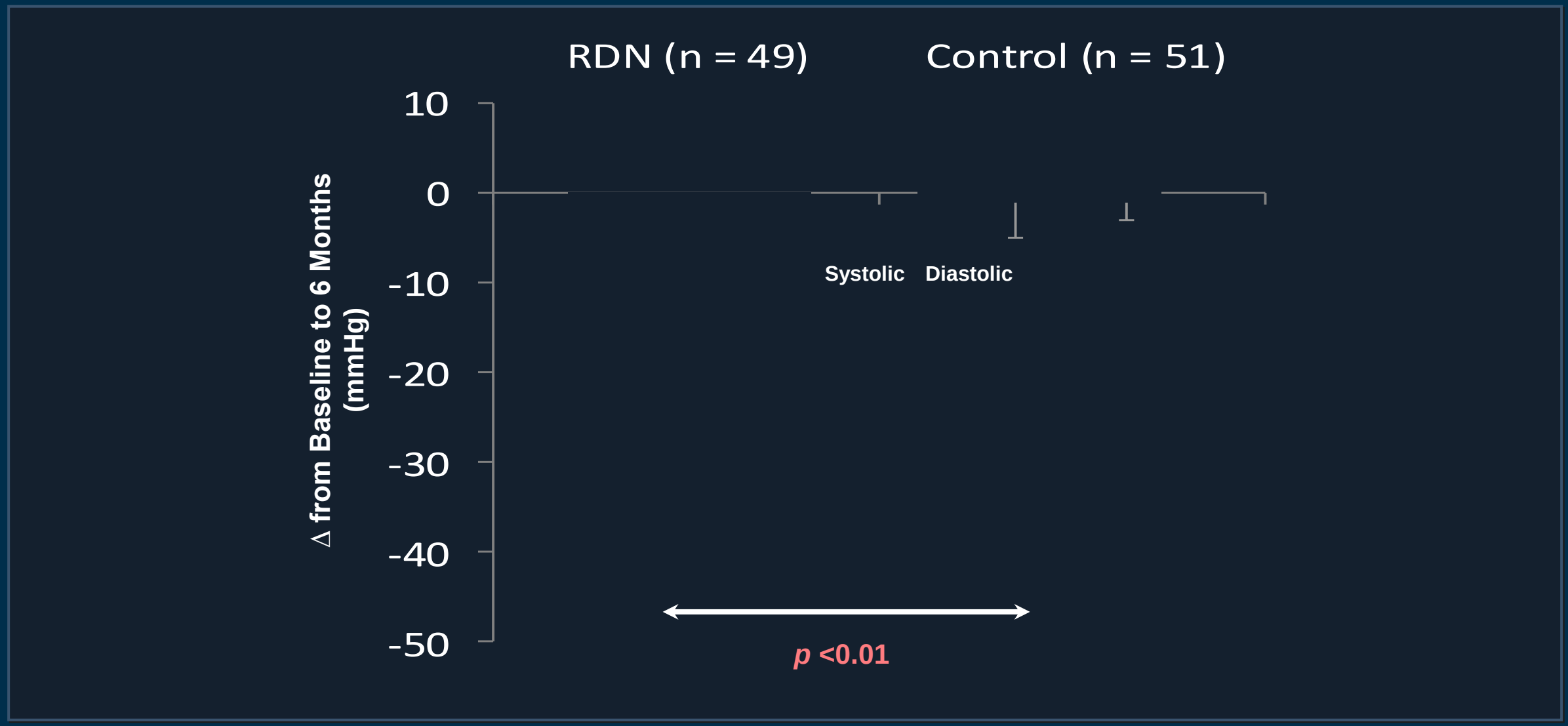
Device Based Therapies

Looking Beyond Conventional Approach

Renal Sympathetic Denervation and BP Reduction

(First Gen Trials)

SYMPLICITY HTN-2: Primary Endpoint



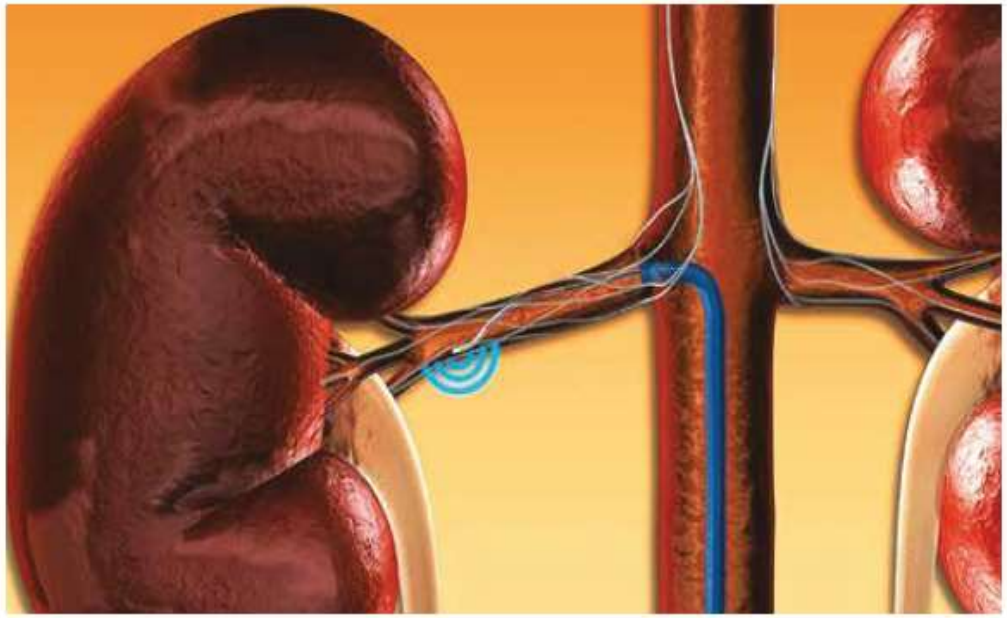
Symplicity HTN-2 Investigators. Lancet 2010; 376: 1903–09

Cardiovascular News

The international newspaper for cardiovascular specialists February 2014 Issue 32

Major setback for renal denervation

Medtronic has announced that the first sham-controlled study of renal denervation—SYMPLICITY HTN-3—has not met its primary efficacy endpoint of significantly reducing blood pressure in patients with severe resistant hypertension and systolic blood pressure of ≥160mmHg. The company has also revealed plans to suspend enrolment in three ongoing regulatory approval trials pending a review of SYMPLICITY HTN-3's findings



In the study, 535 patients (at 87 US medical centres) with treatment-resistant hypertension and systolic blood pressures of ≥160mmHg were randomised to one of three groups—two renal denervation groups and one sham procedure group. The primary efficacy endpoint was the change in office blood pressure from

clinical trial programme.

Pending this panel review, the company has said it plans to suspend enrolment in the three countries where renal denervation hypertension trials are being conducted for regulatory approvals (SYMPLICITY HTN-4 in the USA, HTN-Japan and HTN-India). However, it

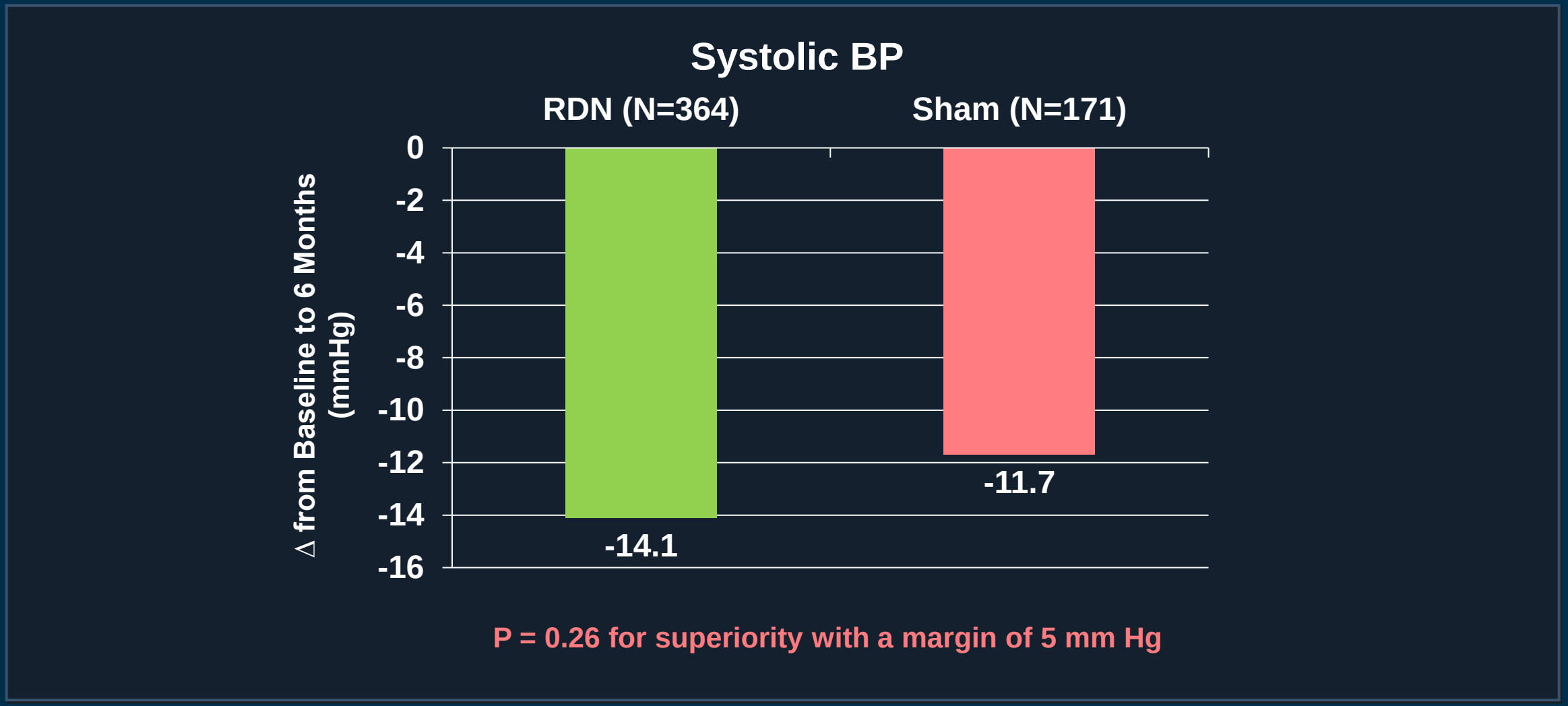
believe this course of action is the most prudent and will

widely believed to be the 2014 American College of

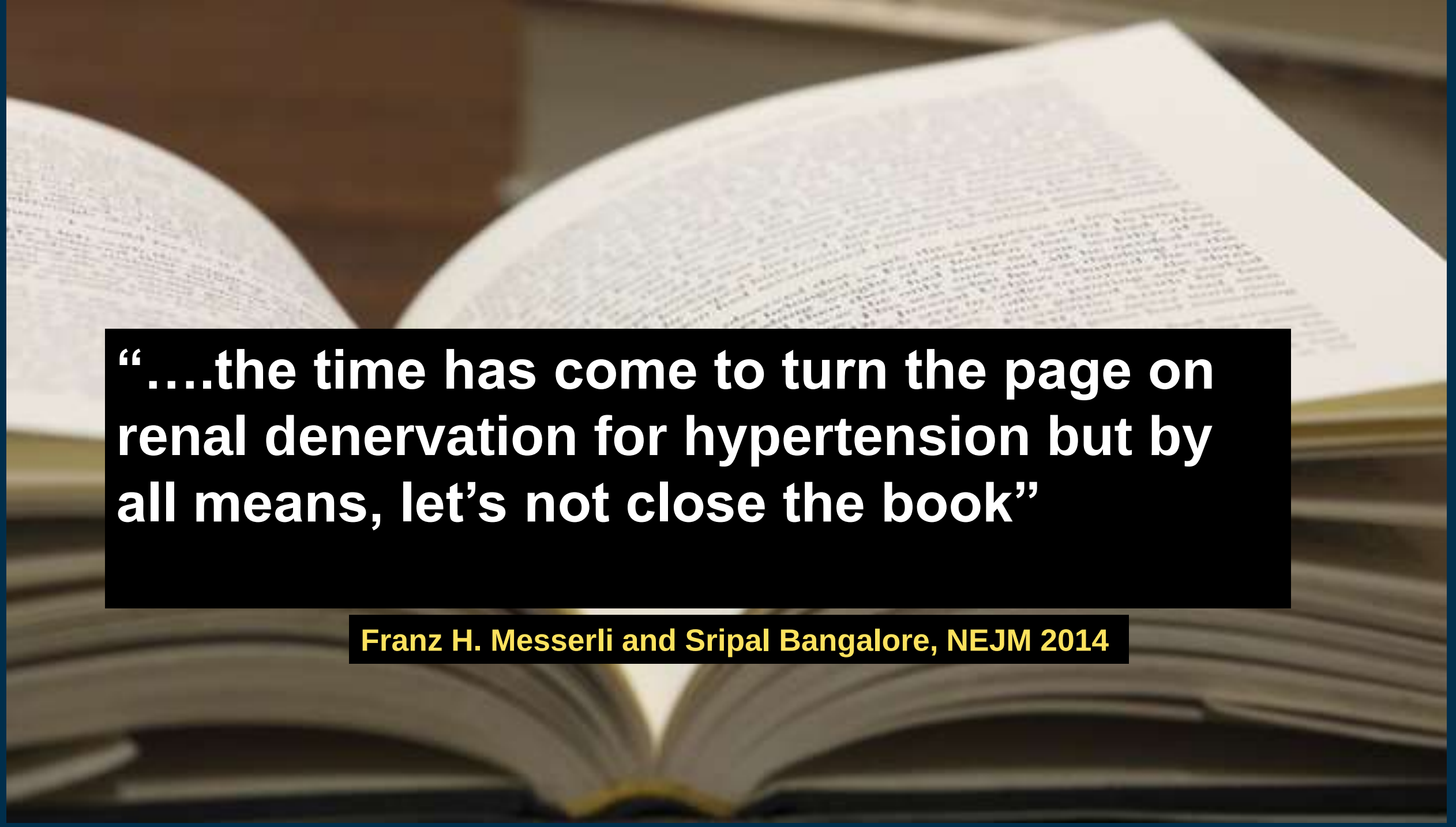
conducted to date, and the first of its kind to include a sham-

SYMPLICITY HTN-3: Primary Endpoint

Office BP at 6 months

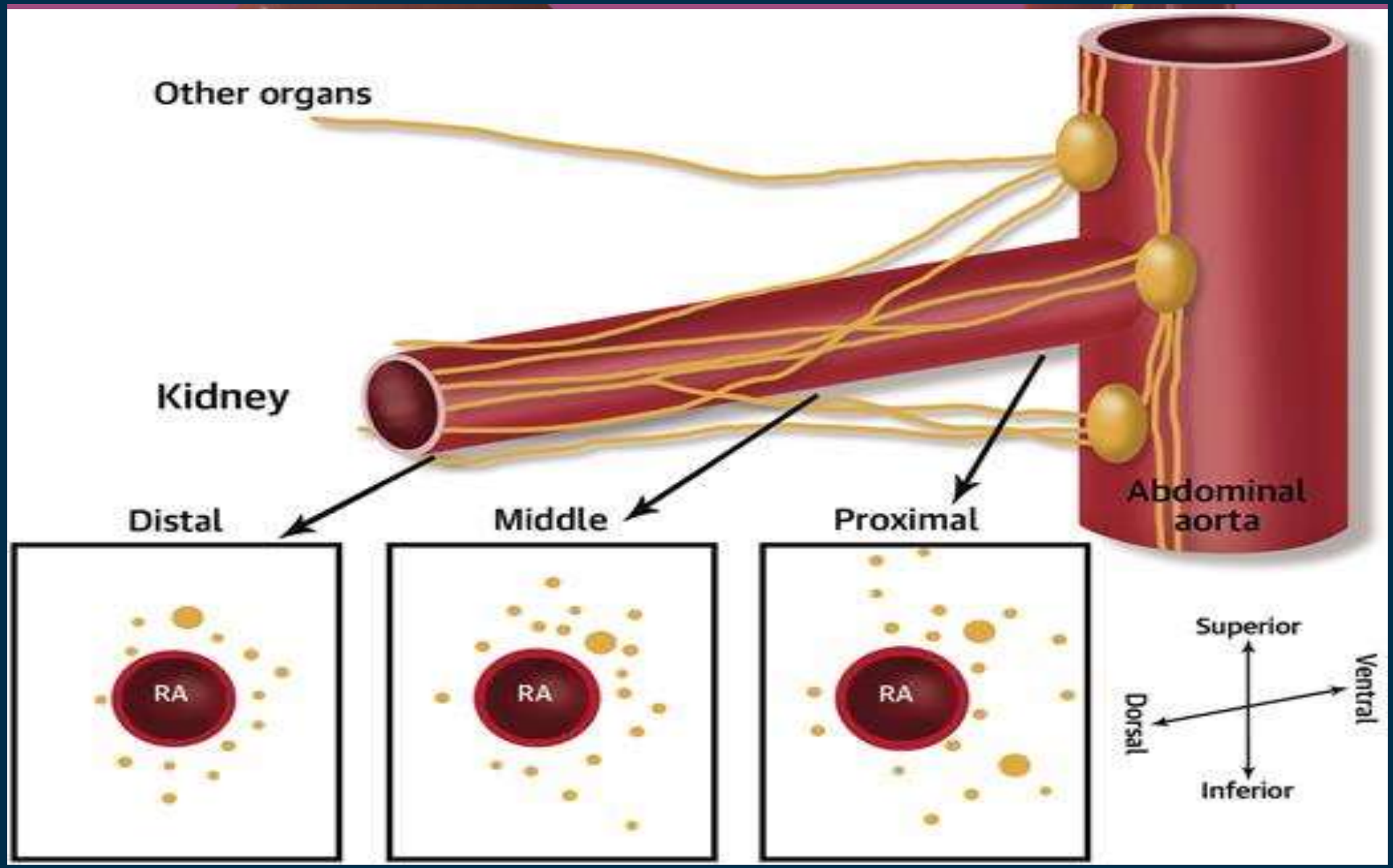


Bhatt et al. N Engl J Med 2014;370:1393-401.

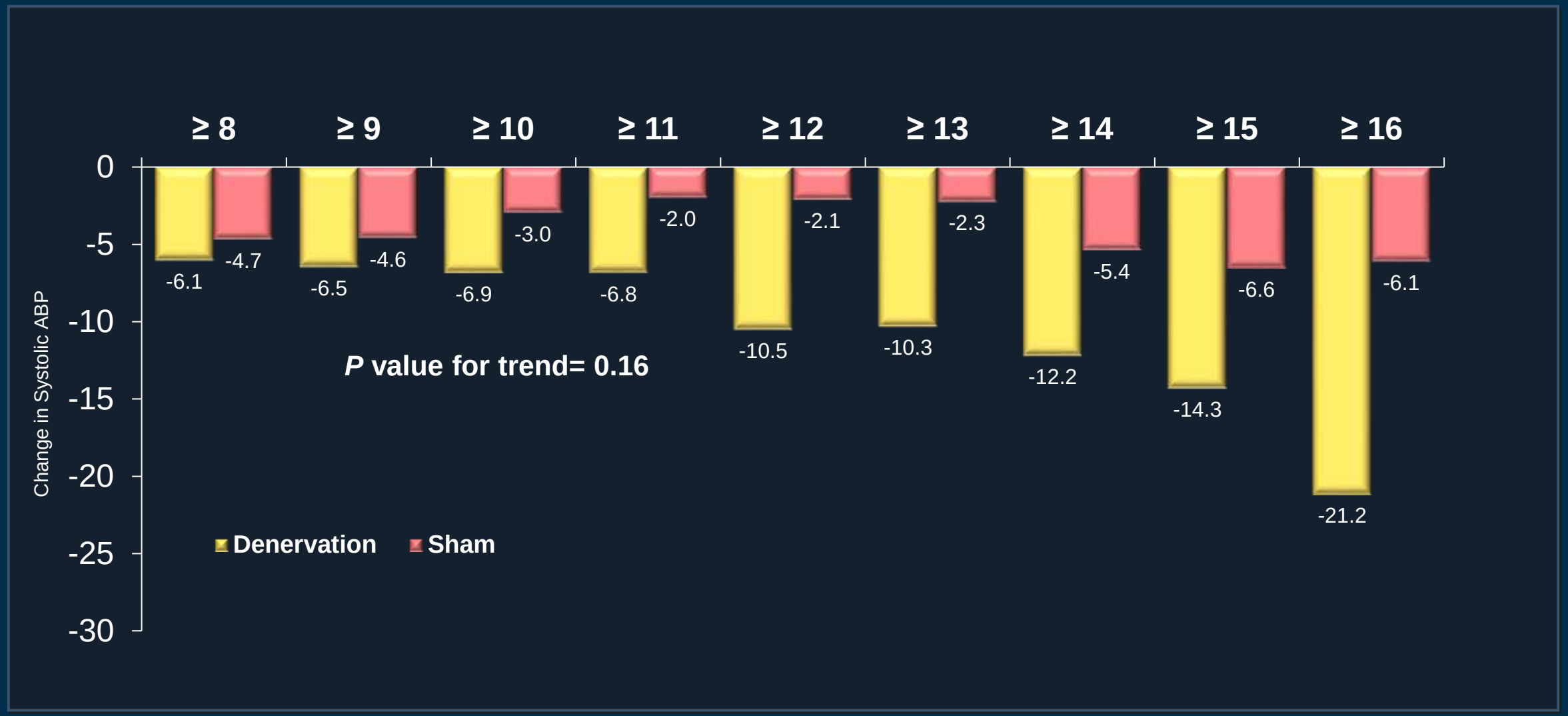

“….the time has come to turn the page on renal denervation for hypertension but by all means, let’s not close the book”
Franz H. Messerli and Sripal Bangalore, NEJM 2014

Lessons Learned From Prior Trials

Variability in Renal Nerve Distribution



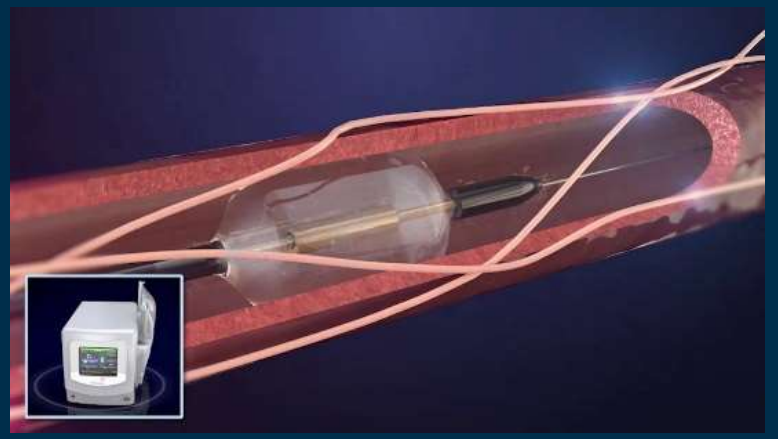
SYMPLICITY HTN-3: Impact of Number of Ablations

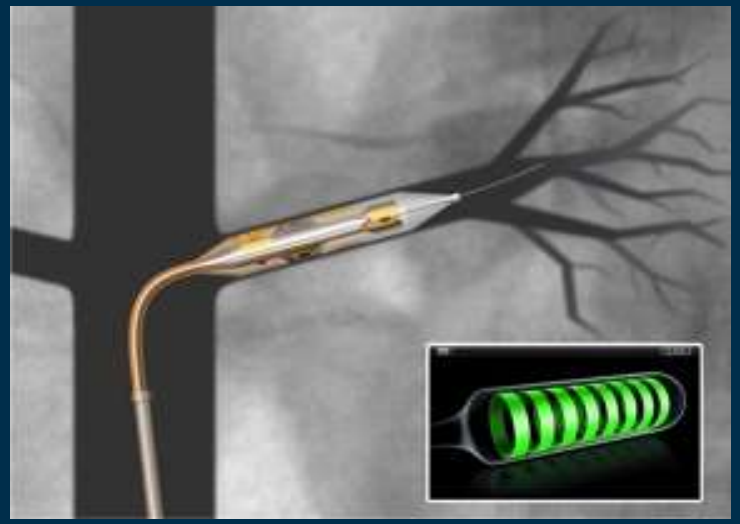


Kandzari D. EuroPCR 2014

RDN for Hypertension

Device Changes



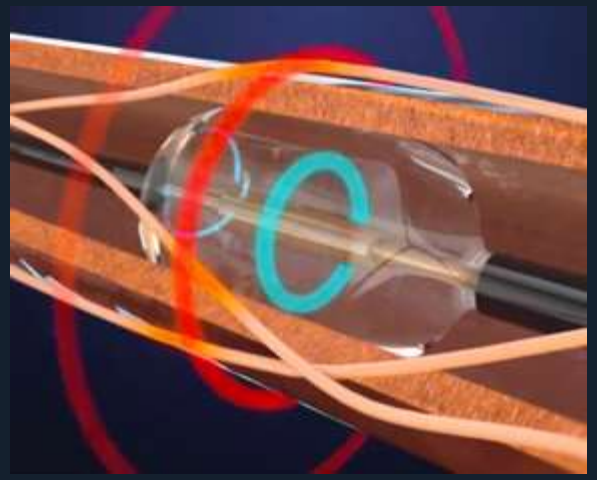


Renal Sympathetic Denervation and BP Reduction

(Second Gen Trials)

Paradise™ Ultrasound Renal Denervation (uRDN) System

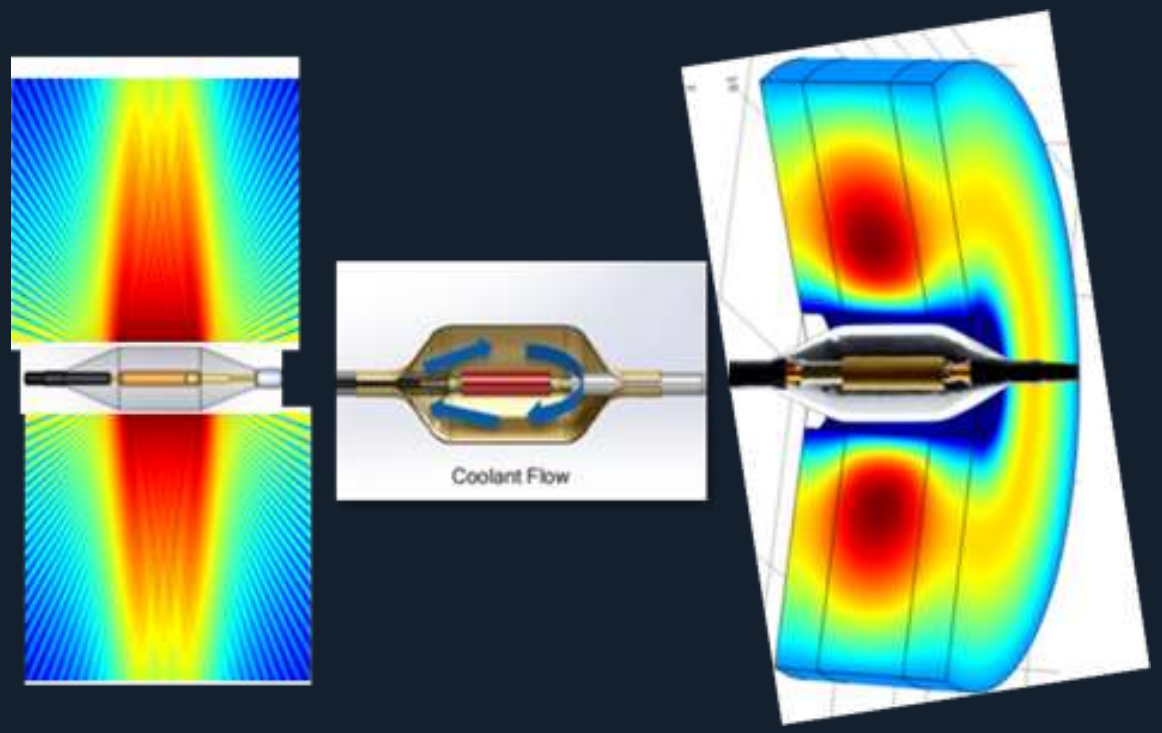
Paradise™ uRDN



- Cool – protect the renal artery from the inside
- Heat – ablate the renal nerves on the outside

Paradise™ Technology

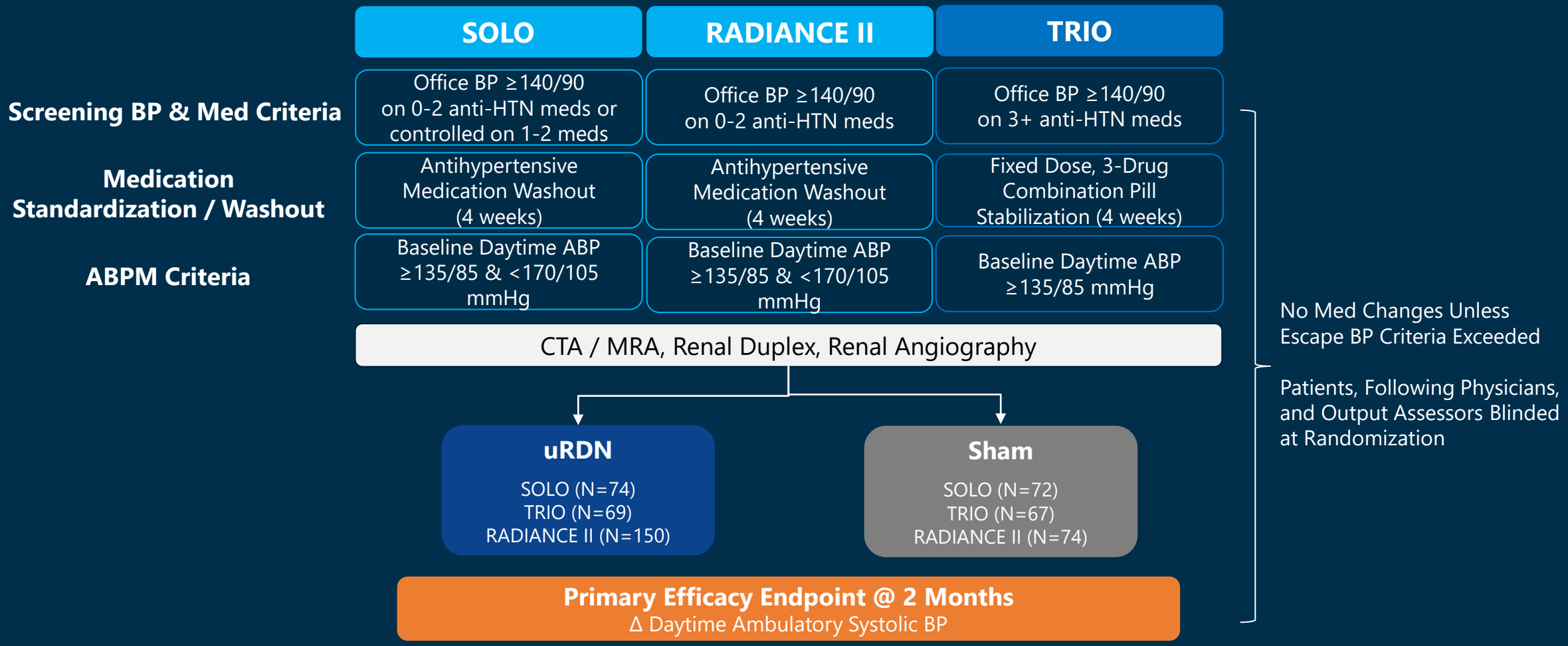
Ultrasonic Heating + Water Cooling → Paradise™ Thermal Profile



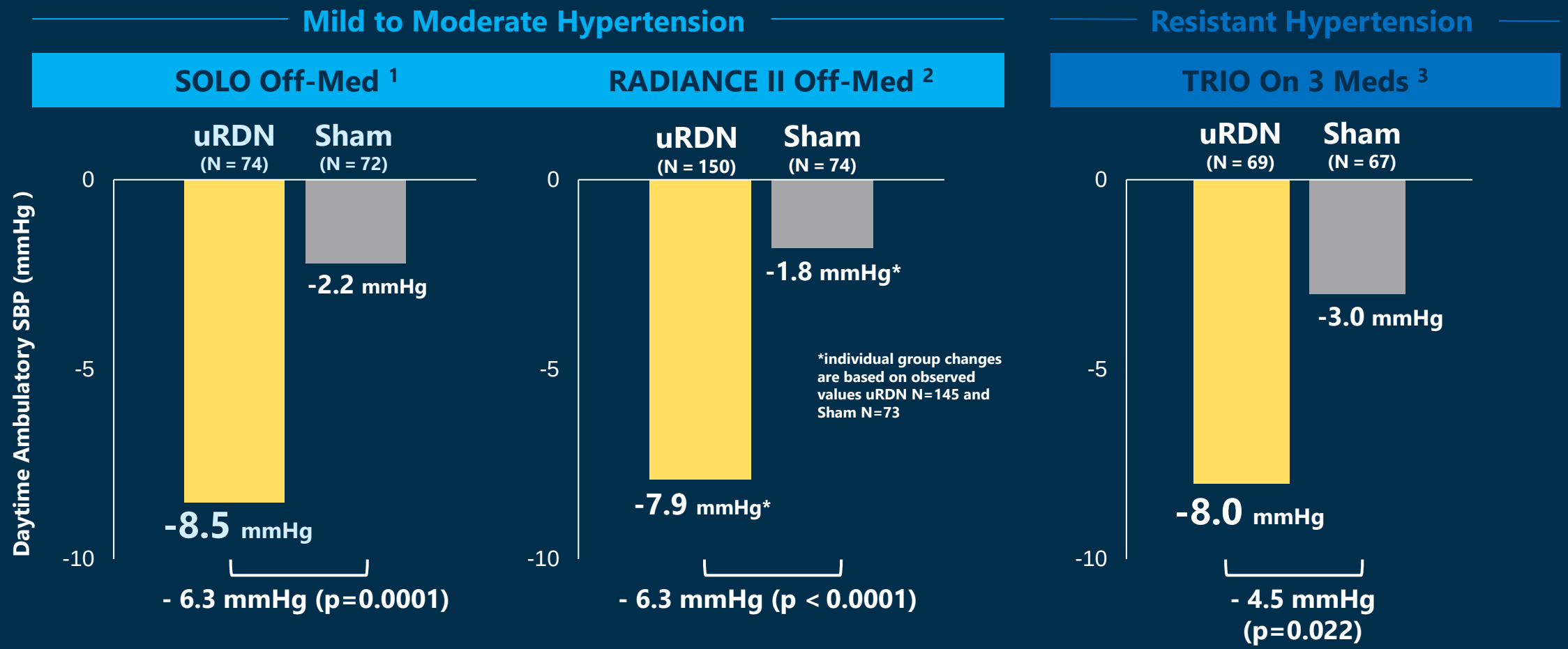
Paradise™ Thermal Profile:
Protect Renal Arteries & Ablate Renal Nerves

RADIANCE™ Study Designs (SOLO, TRIO, RADIANCE II)

Blinded, Sham-Controlled, Individually Powered Trials to Demonstrate BP Lowering Effectiveness at 2 Months

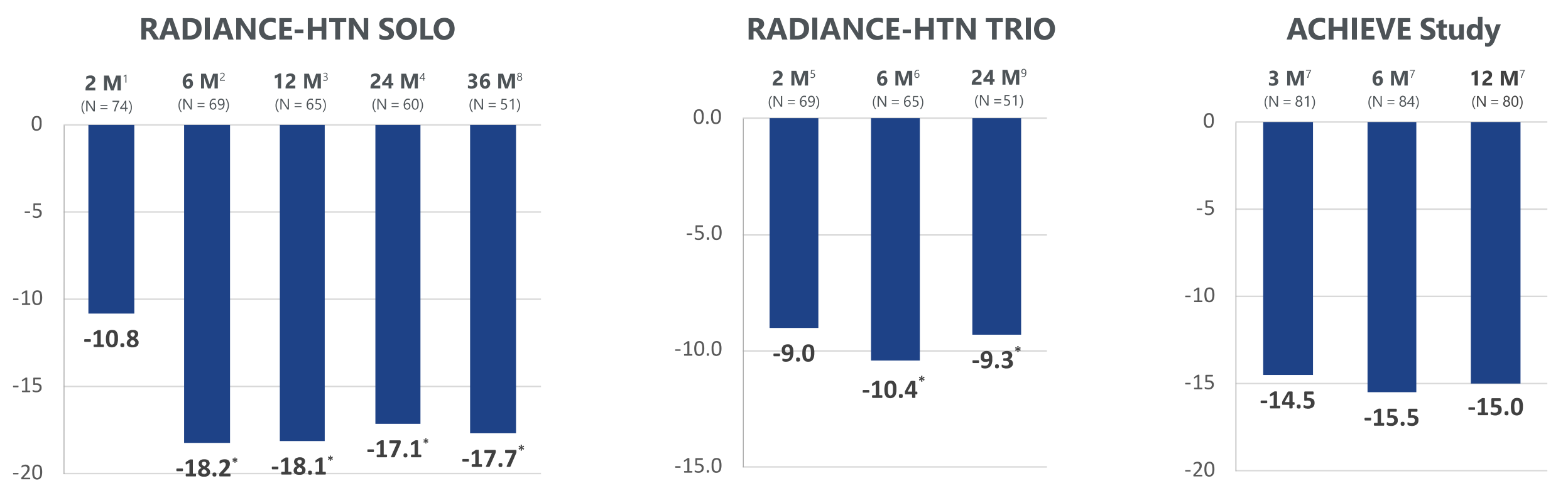


uRDN Demonstrated Significant Blood Pressure Reductions in 3 Sham-Controlled Randomized Trials



1. Azizi et al. *Lancet*. 2018 Jun 9;391(10137):2335-2345. 2. Kirtane et al. TCT2022. 3. Azizi et al. *Lancet*. 2021 Jun 26;397(10293):2476-2486

RADIANCE-HTN and Achieve Studies: Office Systolic Blood Pressure up to 36 Months

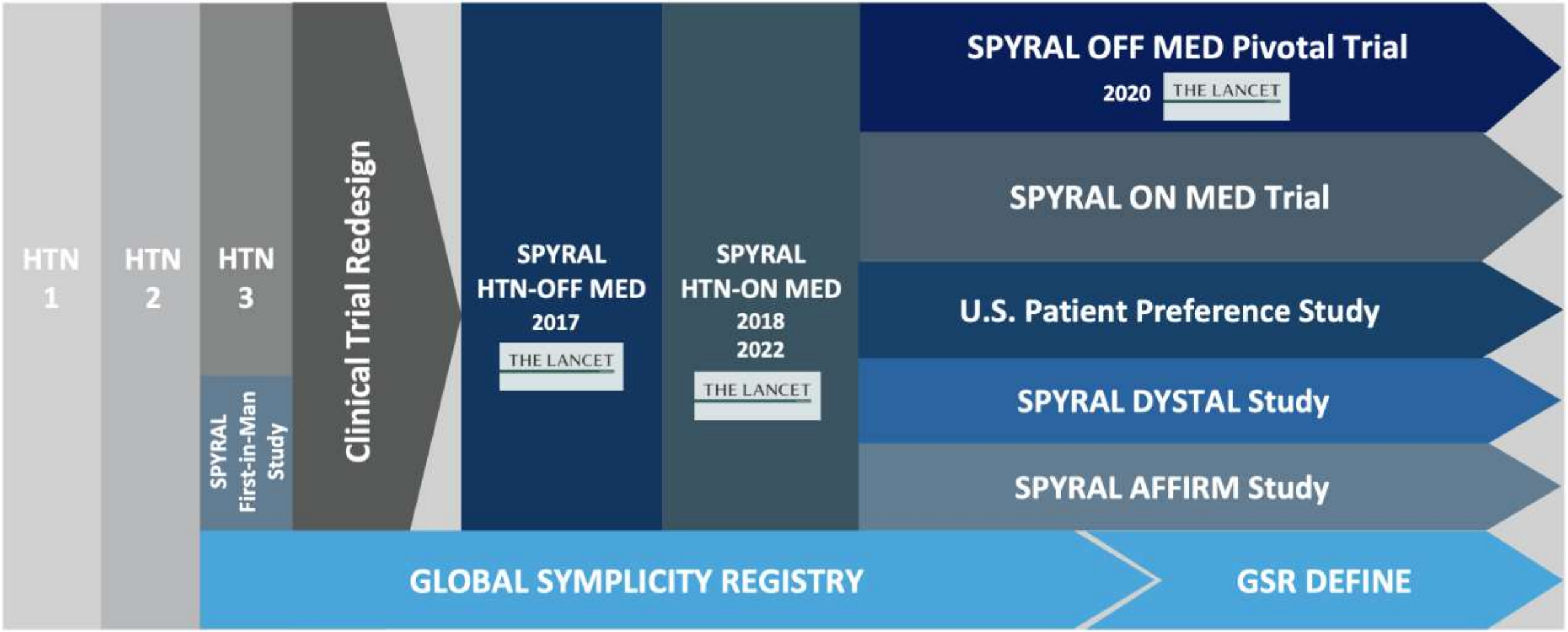


* Medication titrated

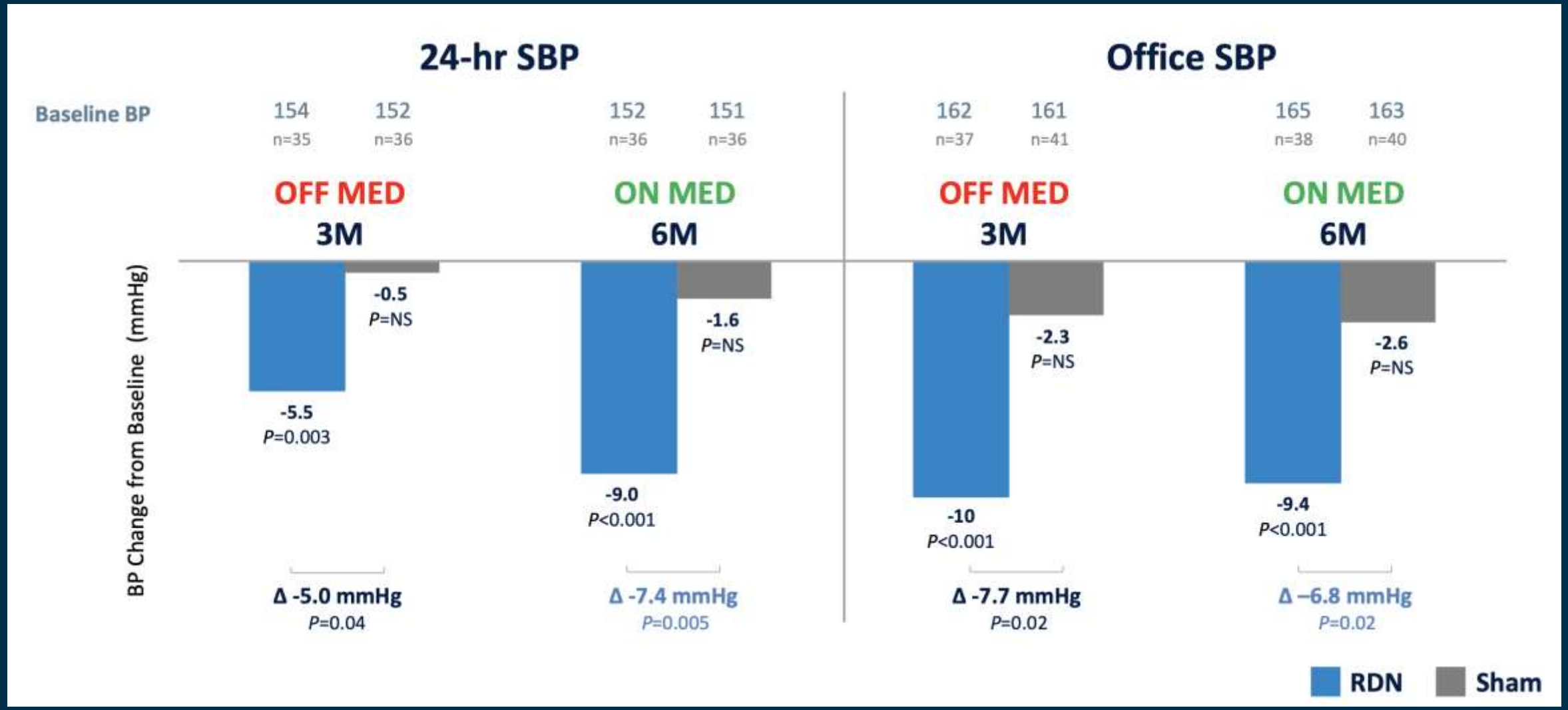
1. Azizi et al. *Lancet*. 2018 Jun 9;391(10137):2335-2345. 2. Azizi et al. *Circulation*. 2019;139:2542–2553. 3. Azizi et al. *JACC Cardiovasc Interv*. 2020 Dec 28;13(24):2922-2933. 4. Rader et al. TCT 2021 5. Azizi et al. *Lancet*. 2021;397:2476-2486. 6. Kirtane et al. TCT 2021. 7. Daemen et al. J *Hypertens*. 2019 Sep;37(9):1906-1912. 8. Rader et al. *EuroIntervention* 2022;18-online 9. Schmieder et al. TCT 2022

SPYRAL HTN Clinical Program

Over 4,000 Patients Studied Across Broad Patient Population



SPYRAL HTN OFF MED and ON MED Pilot Programs



OFF MED Pilot: Townsend, R., et al. The Lancet, 2017
ON MED Pilot: Kandzari, D., et al. The Lancet, 2018

SPYRAL HTN OFF MED and ON MED Pilot Programs

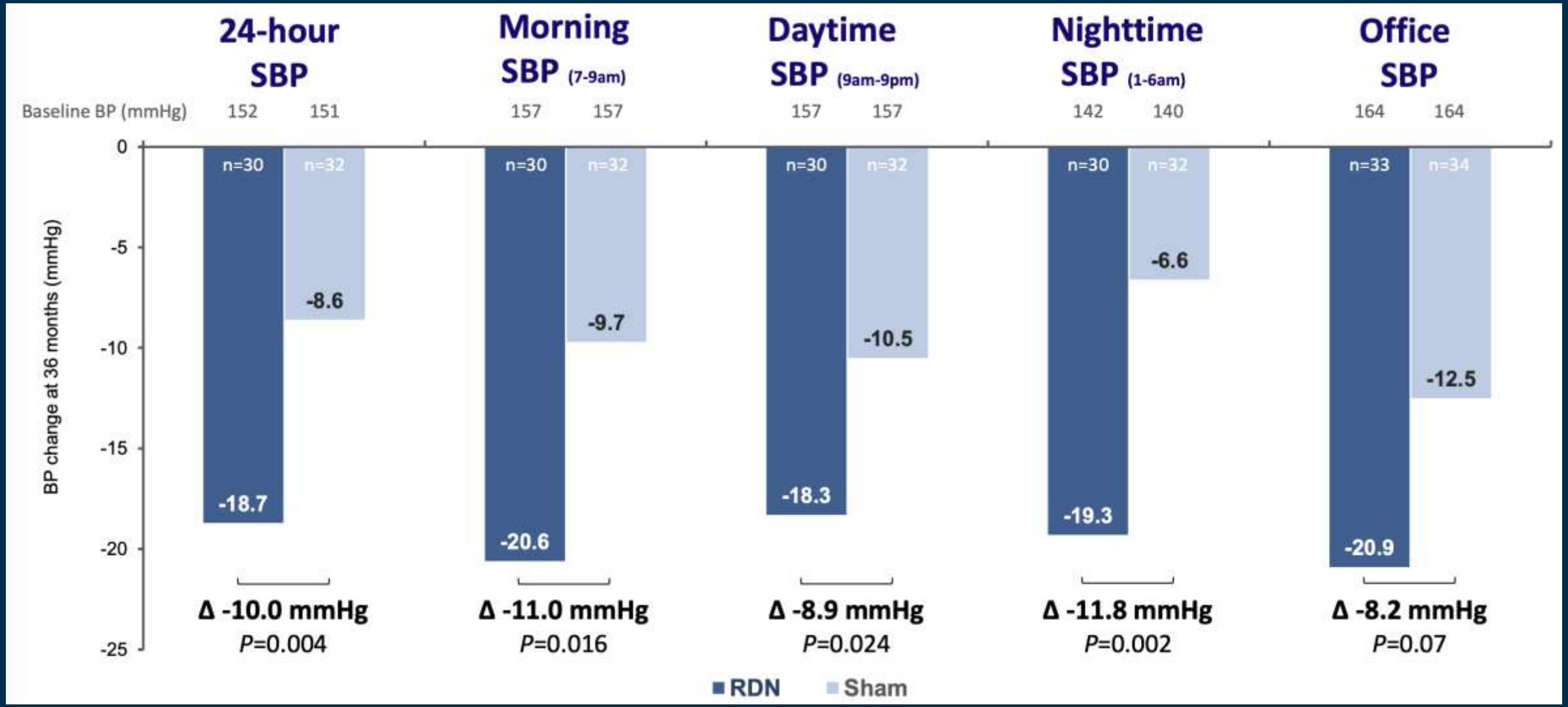
	OFF MED PILOT STUDY[1]		ON MED PILOT STUDY[1]	
Major Adverse Events (%)	RDN (n = 38)	Sham Control (n = 42)	RDN (n = 38)	Sham Control (n = 42)
Death	0	0	0	0
New myocardial infarction	0	0	0	0
Major bleeding (TIMI[2])	0	0	0	0
New onset end stage renal disease	0	0	0	0
Serum creatinine elevation >50%	0	0	0	0
Significant embolic event resulting in end-organ damage	0	0	0	0
Vascular complications	0	0	0	0
Hospitalization for hypertensive crisis/emergency	0	0	0	0
New stroke	0	0	0	0
New renal artery stenosis > 70%	0	0	0	0

1 Time Frame for Evaluation of Adverse Events: From baseline to 1 month post-procedure (6 months for new renal artery stenosis)
2 TIMI definition: intracranial hemorrhage, ≥5g/dl decrease in hemoglobin concentration, a ≥15% absolute decrease in hematocrit, or death due to bleeding within 7 days of the procedure.

OFF MED Pilot: Townsend, R., et al. The Lancet, 2017
ON MED Pilot: Kandzari, D., et al. The Lancet, 2018

SPYRAL HTN ON MED Pilot

3 Year Follow-up

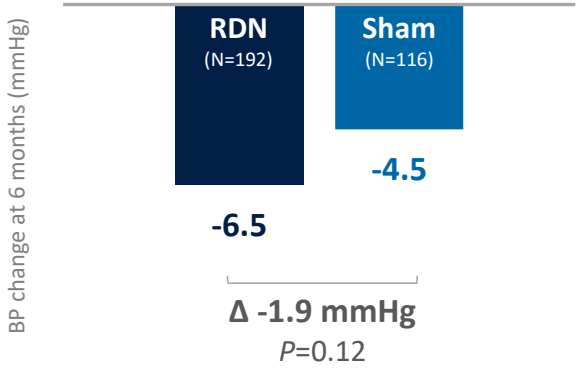


Mahfoud F, Kandzari D, et al. *Lancet 2022;* ACC Late Breaking Trials 2022

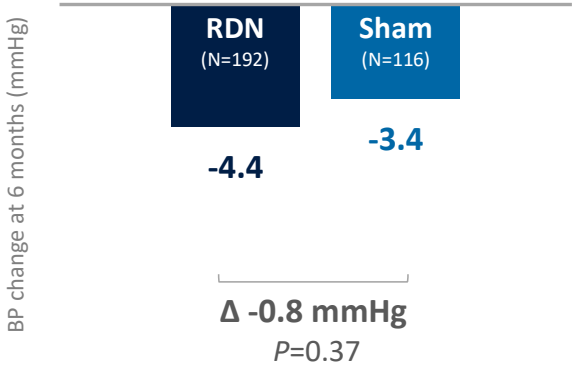
SPYRAL HTN ON MED Pivotal Trial

Blood Pressure Changes at 6 Months

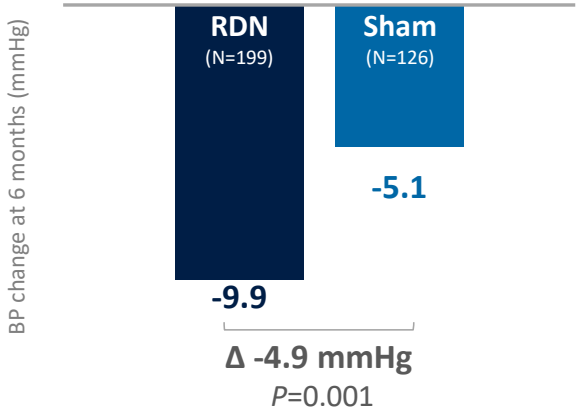
24-hr Systolic ABPM



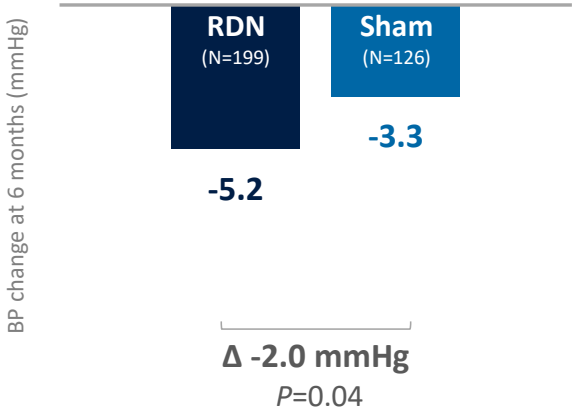
24-hr Diastolic ABPM



Office Systolic BP

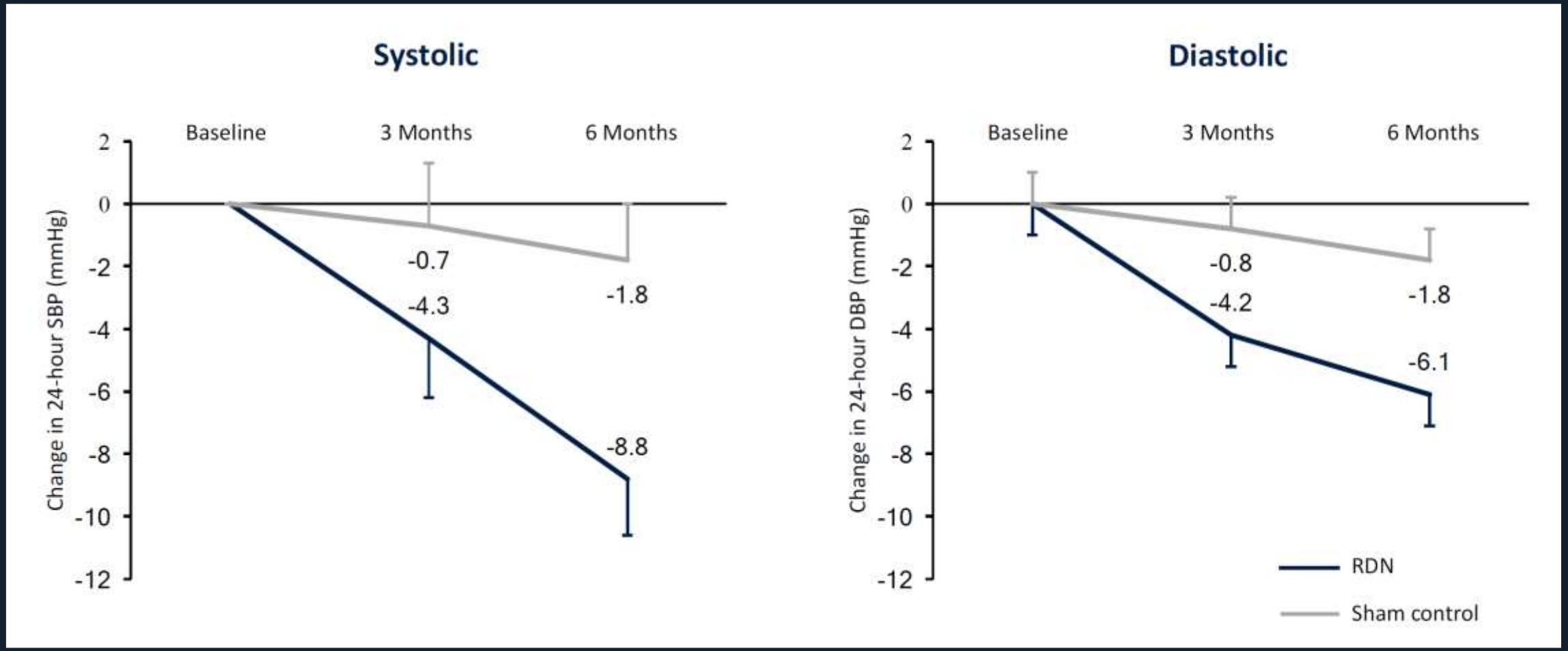


Office Diastolic BP



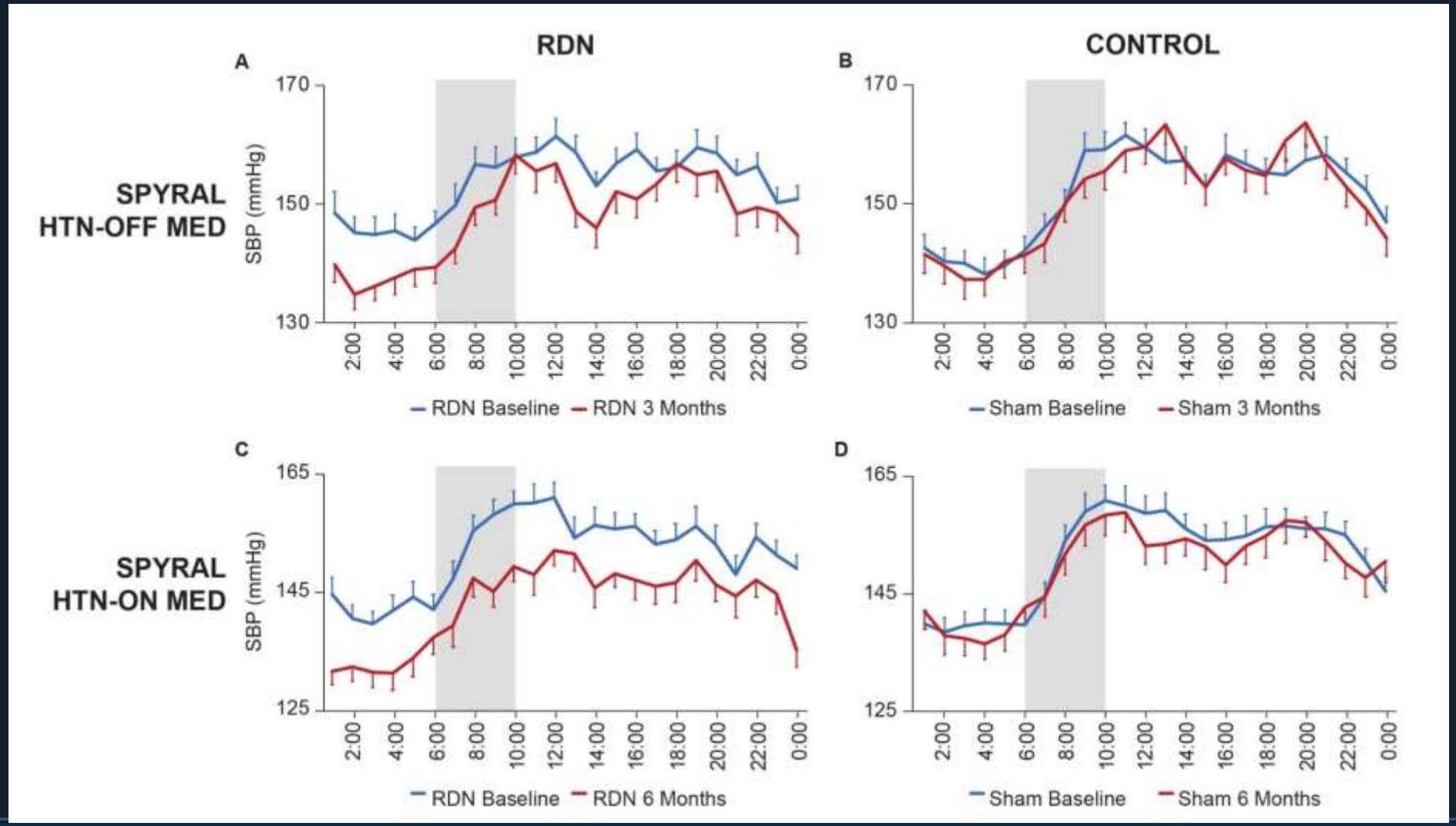
AHA Late Breaking Trials 2022

SPYRAL ON MED: BP Response over Time



Kandzari D, et al. Lancet. 2018

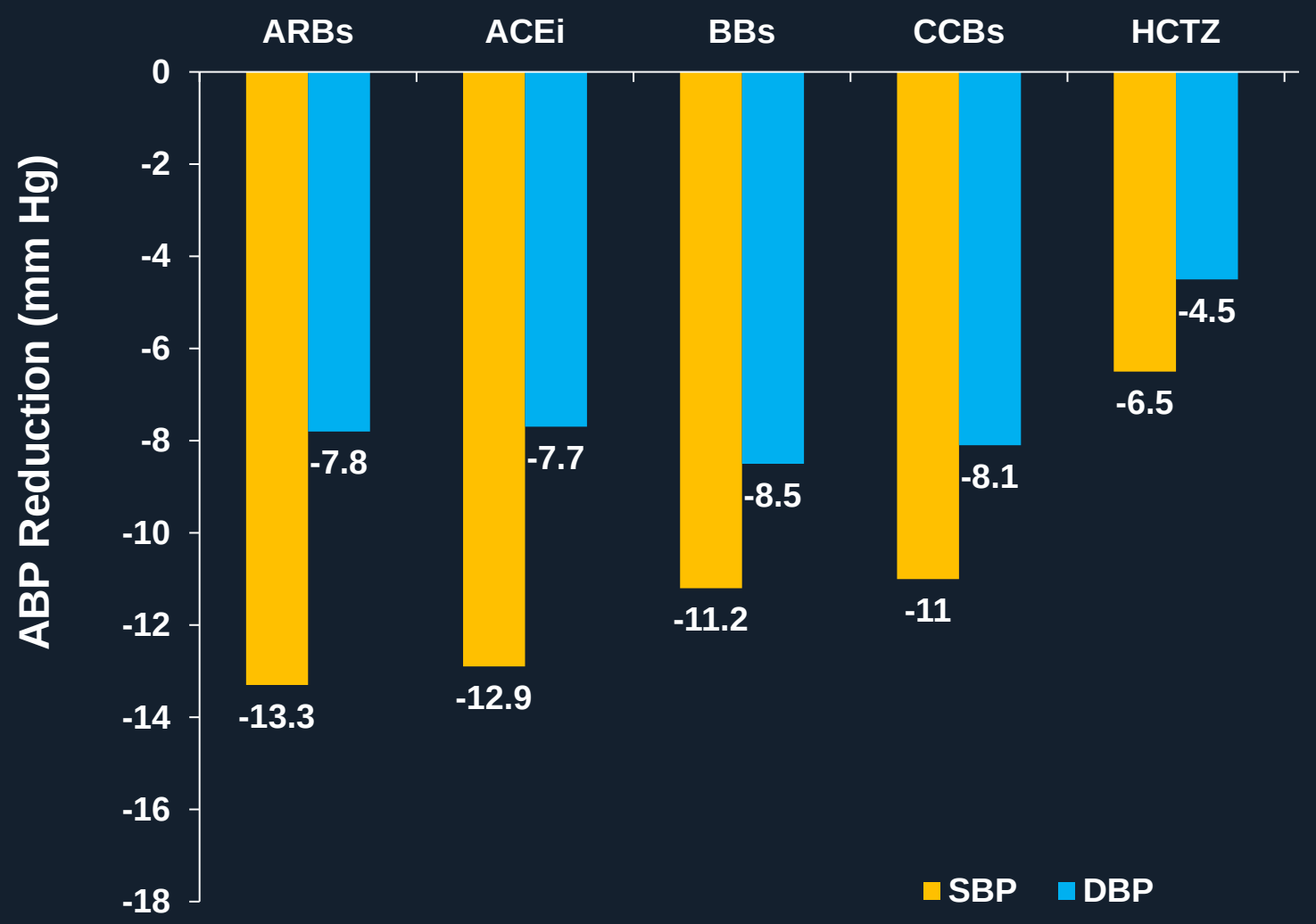
RDN Effect on BP: “Always On”



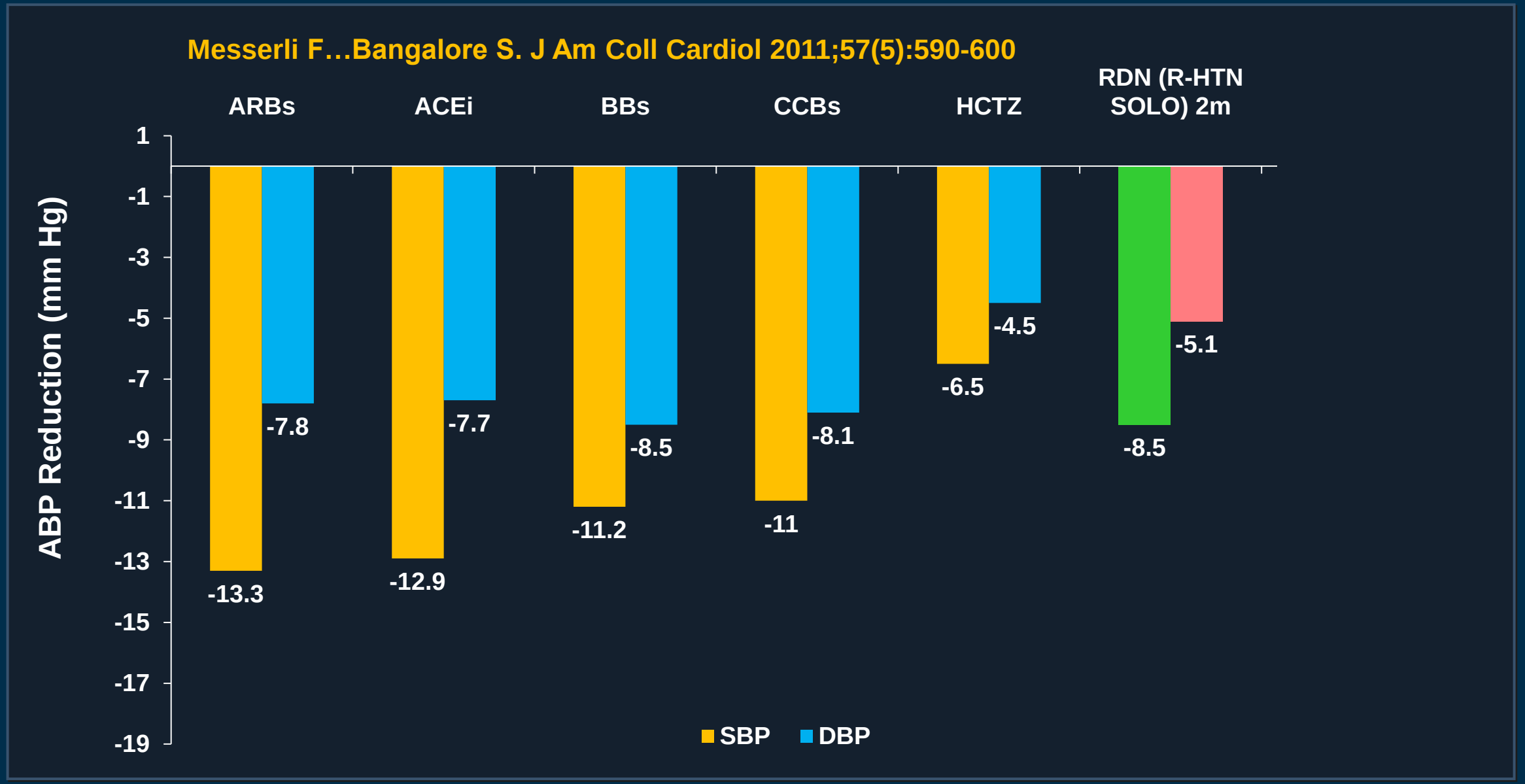
Kario K, et al. Hypertension. 2019 Jul 1:HYPERTENSIONAHA11913081.

ABP Reduction: Comparison to Medications

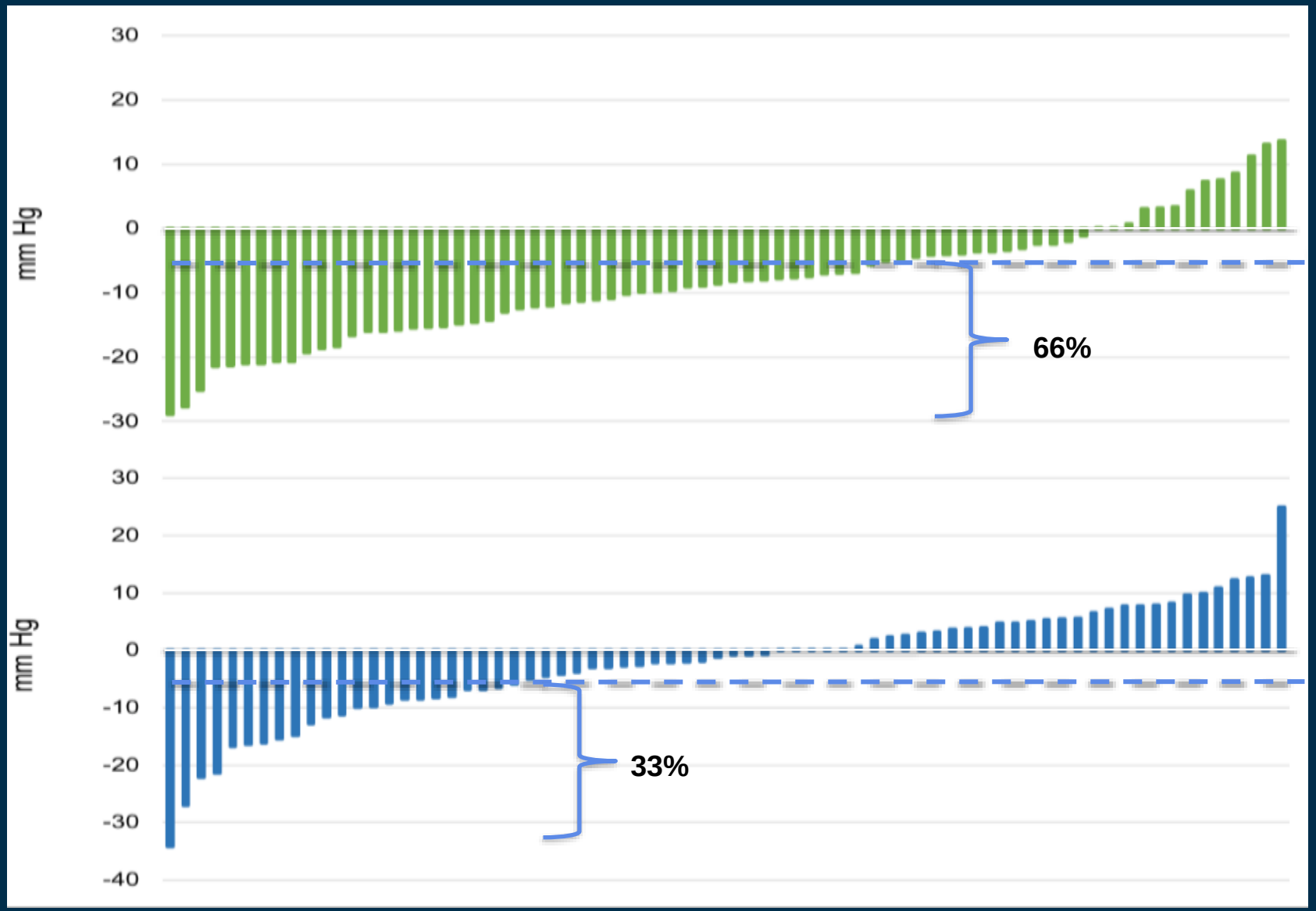
Messerli F…Bangalore S. J Am Coll Cardiol 2011;57(5):590-600



ABP Reduction: Comparison to Medications



RDN: Individual Patient Response



% Patients with
≥ 5 mm Hg Decrease

Renal Denervation: 66%
Sham Procedure: 33%

P<0.001

Azizi et al. Lancet. Published online 23 May 2018

RDN for Hypertension

Summary and Unanswered Questions

- RDN is safe with very low risk of complications
- RDN lowers BP and has an “always on” effect
  - *Long-term (>5 years) durability of BP reduction unknown*
- RDN decreases pill burden
- BP lowering efficacy of RDN variable
  - *Pre-selection of patients?*
  - *How to test if denervation is achieved?*
  - *How much denervation is optimal?*
- Will BP reduction with RDN provide outcomes benefit?

RDN for Hypertension:

Potential Applications

- Patients with uncontrolled hypertension
- Patient intolerant to antihypertensive agents
- As a first line therapy in patients with sympathetically mediated hypertension (such as the young)

RDN Hype Cycle